MICHIGAN DEPARTMENT OF ENVIRONMENT, GREAT LAKES, AND ENERGY

INTEROFFICE COMMUNICATION

TO: File for 2,4,6,8-tetramethylcyclotetrasiloxane (CAS No. 2370-88-9)

FROM: Mike Depa, Toxics Unit, Air Quality Division

DATE: August 9, 2021

SUBJECT: Screening Level Derivation Update

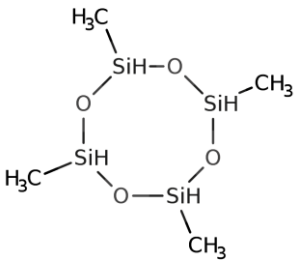
Summary
The initial threshold screening level (ITSL) for 2,4,6,8-tetramethylcyclotetrasiloxane is 100 µg/m^3 (annual).

Previously the ITSL for 2,4,6,8-tetramethylcyclotetrasiloxane was 0.1 µg/m^3 (annual) (DEQ, 1998).

The literature was searched to find relevant data to assess the toxicity of 2,4,6,8-tetramethylcyclotetrasiloxane (TMCTS). The following references or databases were searched: U.S. Environmental Protection Agency (EPA) Integrated Risk Information System (IRIS), Registry for Toxic Effects of Chemical Substances (RTECS), American Conference of Governmental and Industrial Hygienists (ACGIH) Threshold Limit Values (TLVs), National Institute for Occupational Safety and Health (NIOSH) Recommended Exposure Levels (RELs), International Agency for Research on Cancer (IARC) Monographs, Chemical Abstract Service (CAS) SciFinder, European Chemical Agency (ECHA), CompTox Chemicals Dashboard, Provisional Peer-Reviewed Toxicity Values, ChemID*plus* and the U.S. National Toxicology Program (NTP).

The EPA has not established a reference dose (RfD) or a reference concentration (RfC) for TMCTS. There are no occupational exposure limits for TMCTS.

Uses and Physical Chemical Properties
TMCTS is used as an intermediate in synthesis of polysilicones or other cyclic silicones. The molecular structure is shown:



Molecular Formula: C4-H16-O4-Si4
Molecular Weight (MW): 240.51g/mol
SMILES: C[SiH]1O[SiH](C)O[SiH](C)O[SiH](C)O1

Physical Values 2,4,6,8-tetramethylcyclotetrasiloxane (CompTox, 2021)

Property	Predicted Average	Unit
Melting Point	-80.4	°C
Boiling Point	136	°C
Density	1.01	g/cm^3
Vapor Pressure*	5.17	mmHg
LogKoa: Octanol-Air	3.27	-
Henry's Law	8.68	atm-m^3/mole
LogKow: Octanol-Water	4.81	-
Water Solubility	1.96E-03	mol/L

*Similar to ECHA value of 479 pa (0.479 kpa or 3.59 mmHg) (ECHA, 2021)

TMCTS is expected to be volatile because the vapor pressure is >0.1 mmHg and Henry's Law is greater than 1E-5 atm-m^3/mole.

Acute Inhalation Toxicity (ECHA,2021)

In a Lethal Concentration 50% (LC50) study, a group of 10 (5 male and 5 female) Sprague-Dawley rats was exposed for 4-hours to a whole-body vapor of 5 mg/l (5000 mg/m^3) TMCTS.

Sprague-Dawley, Crl:CD(SD)IGS;
Animals at start of study: age 9 weeks;
Body weights females 201.8 - 227.7 grams;
Body weights males 298.1-334.5 grams;
Measured concentration: 445 ppm= 4900 mg/m^3

Conclusion for the LC50 study: The test substance is a mixture of the submission substance, 2,4,6,8-tetramethylcyclotetrasiloxane (CAS 2370-88-9) and 2,4,6,8,10-pentamethylcyclopentasiloxane (CAS 6166-86-5). The authors stated that:

> These substances are structurally very closely related and, as shown in the hydrolysis test will probably result in similar or identical hydrolysis product in contact with water. The results for the mixture are therefore considered to be applicable to both substances individually. No mortality was seen after a 4-hour exposure to a mean measured concentration of 4.9 mg/l or during a 14-day observation. The LC50 is considered to be greater than 4.9 mg/l.

REPRODUCTIVE/DEVELOPMENTAL TOXICITY (ECHA, 2021)

In a reproductive/developmental toxicity study, groups of 10 male and 10 female Wistar rats (RccHan:WIST(SPF)) were exposed via whole body inhalation (vapor) for 6 hrs per day to 0, 100, 1000, 3000 ppm. Due to excessive mortality at 3000 ppm of 3 females and 1 male at the higher dose this dose group's exposure concentration was reduced to 2000 ppm. The duration of exposure was at least 28 days for males and up to approximately 7 weeks for females. Weight at study initiation: Males: 266-347g; Females: 181-225g. The 3000 ppm dose is equivalent to 29510 mg/m^3 and is based on a molecular weight of 240.5094 for TMCTS. The protocol of the study was conducted

according to OECD 422 (Combined Repeated Dose Toxicity Study with Reproduction/Developmental Toxicity Screening in the Rat).

RESULTS: Maternal toxic effects: yes. Details on maternal toxic effects: Reduced body weight gain and reduced food consumption during pre-pairing period. Adverse renal and urinary tract pathology. Also, pathology changes in heart, liver, lung and adrenal gland were all noted at 3000/2000 and at the 1000 ppm dose.

No effects on development were observed up to the highest dose level, therefore, the NOAEL (no-observed-adverse-effect-level) for development was considered to be 2000 ppm (equivalent to 19674 mg/m^3).

Summary: In a well-conducted, GLP compliant, OECD 422 study (reliability 1) treatment with the test item at the dose level of 3000 ppm caused early death of three females. After reduction of the high-dose level to 2000 ppm, two further females were found dead. Uremia resulting from the impairment of the urinary tract was indicated as a cause of the early deaths. The early deaths of animals might be due to the initial higher exposure to the test item at the concentration of 3000 ppm. All remaining animals survived the scheduled study period.

Treatment with TMCTS caused a reduction of food consumption in males at all dose levels and in females at the dose level of 3000/2000 ppm. Body weight gains and body weights were reduced at the dose level of 3000/2000 ppm in both sexes. Effects on food consumption, body weight gain and body weights were considered not to be adverse. Also, pathology changes were observed in heart, liver, lung and adrenal gland, all noted at 3000/2000 and 1000 ppm.

At the 2000 ppm dose level it was noted there was a lower number of corpora lutea. As a consequence, a lower implantation rate and a lower number of living pups at first litter check were noted. Although the differences to the control values were not statistically significant, they were below the range of the historical control values and were therefore considered to be related to the treatment with the test item. These effects occurred at the dose level at which severe maternal toxicity was noted early on in the study and therefore may be secondary to the maternal toxicity. The authors stated that both possibilities could be true: a reduction of corpora lutea as a specific effect of the test item or as an effect secondary to the maternal toxicity may be taken into consideration. In order to be health protective, the reduction of the number of corpora lutea and consequent reduction of number of pups was determined to be an adverse effect at the 2000 ppm dose level (lowest-observed-adverse-effect-level; LOAEL). The authors stated that, “higher body weights and body weight gain of pups was noted at the high-dose level indicating that the development of pups was not affected by the treatment.” The reproductive NOAEL is 1000 ppm.

The authors states that there were no observed effects on development up to the highest dose level, and therefore the NOAEL for developmental effects was considered to be 2000 ppm (equivalent to 19674 mg/m^3).

Additional findings: Treatment-related microscopic findings were observed mainly in the urinary organs in both sexes, both in the survivors and decedents, at the dose levels of

1000 and 3000/2000 ppm. The thyroid gland (surviving males) and heart (decedent females) were also considered to be the main target organs.

In the kidney, the following findings were noted in both sexes at the dose levels of 1000 and 3000/2000 ppm or only at the dose level of 3000/2000 ppm: granular deposits in the pelvis and in the tubules, pyelitis (with foreign-body granuloma), urothelial hyperplasia and ulcer/erosion, tubular simple dilation, increased mitoses in the tubular epithelium, pelvic dilation, tubular basophilia, hyaline droplets and mononuclear cell foci. Specific to decedent animals, tubular necrosis/degeneration and slight papillary necrosis, pelvic dilation, tubular basophilia and tubular simple dilation were mainly observed. Granular deposits in the pelvis, pyelitis (with foreign-body granuloma) and urothelial hyperplasia and ulcer/erosion were observed with a low frequency. Fibrosis, inflammatory cell infiltration and mononuclear cell foci were also observed.

In the ureter, the following findings were observed at the dose level of 3000/2000 ppm: granular deposits in the lumen (in males), inflammatory cell infiltration (in males) and luminal dilation (in males and females). Luminal dilation and inflammatory cell infiltration in the surrounding soft tissue were observed in decedent animals.

In the urinary bladder, the following findings were observed at the dose levels of 1000 and 3000/2000 ppm in both sexes: urothelial hyperplasia and increased inflammatory cell infiltration (with foreign-body granuloma) and at the dose level of 3000/2000 in both sexes: granular deposits in the cavity or submucosa, hemorrhage, ulcer, and edema (only in males).

In the urethra, marked injury was observed specifically to the decedent females. Granular deposits, necrosis involving the mucosa, submucosa and surrounding tissues, inflammatory cell infiltration, luminal dilation and urothelial hyperplasia were observed in the urethra of all decedent females.

Treatment-related findings in the heart were specific to the decedents. Myocardial necrosis/degeneration, inflammatory cell infiltration, fibrosis, myocardial mineralization and hemorrhage were observed.

Urinary obstruction was indicated in most of the decedent animals by the marked luminal distention of the urethra, distention with urine of the urinary bladder (macroscopically), luminal distention of the ureter, pelvic dilation, and tubular simple dilation of the kidney. The authors stated that this was probably caused by the existence of the calculi or the injury including necrosis and inflammation at the lower urinary tract (urethra). Urinary obstruction might have caused uremia and subsequent death. The remarkable heart lesions observed in this study might have caused heart failure and thereby also been the direct cause of death. The heart lesions observed in the decedents can be induced by uremia.

At the end of the recovery period, similar kidney, urinary bladder, and urethral findings were still noted and myocardial necrosis/degeneration, inflammatory cell infiltration and fibrosis was noted in one male.

In the thyroid gland, amorphous materials in the colloid were observed in males of all treatment groups with dose-dependency in its severity and incidence. No further indicators of thyroid injury (necrosis, apoptosis, fibrosis, other degenerative changes, etc.) were noted. This change was considered to have been caused by metabolic change in the thyroid and was not noted at the end of the recovery period.

At the dose level of 3000/2000 ppm, treatment-related findings in the liver, hepatocellular hypertrophy and increased mitoses were found in decedents. Hepatocellular hypertrophy was macroscopically correlated with enlargement of the organ. The authors stated that the significance of these changes remains unknown.

Testicular tubular degeneration found in two males at each dose level of 100 and 1000 ppm and in four males at the dose level of 3000/2000 ppm was in most cases unilateral and within the range of historical control data. This effect was also noted in both decedent males in the recovery group. The marked renal lesions may have caused inanition making effects on the testes of these decedents. The authors reported, “Alveolar edema in the lung and congestion in the several organs were observed only in the decedent animals. Although these can be agonal or postmortem changes, the possibility of the secondary changes associated with the heart disorder or uremia cannot be excluded.” It was assumed that the authors found these effects in the 2000 ppm TMCTS group.

Cortical hypertrophy of the adrenal gland (macroscopically correlated with enlargement of the organ), atrophy of the spleen (macroscopically correlated with reduction in size of the organ) and atrophy of the thymus and ulcer in the forestomach (macroscopically correlated with mucosal crateriform retractions) were observed only in the decedent animals. The authors stated that, “No other related findings were observed in the same organs and therefore, these changes were considered to be the secondary effect caused by stress.” Atrophy of the spleen and thymus were considered adverse effects due to exposure. The dose level these effects occurred at were not specified, however, it was assumed to be 2000 ppm TMCTS.

In the vagina, mucification with mucus plug was observed in the decedent females. The authors stated that this change may have been caused by the stimulation by the marked inflammatory changes that occurred in the urethra or associated with the possible inanition caused by the renal lesions in these animals.

No neoplastic were effects observed.

The NOAEL was found to be 100 ppm in both male and female rats. The authors stated that the basis for the effect level was, “Bladder stones and histopathological findings in the urinary tract at 3000/2000 and 1000 ppm, plus reversible reduction of food consumption and reversible pathology change in thyroid gland in males at 100 ppm.” Pathology changes were observed in heart, liver, lung and adrenal gland, all noted at 3000/2000 and 1000 ppm. The 100 ppm dose is equivalent to 984 mg/m^3 based on MW of 240.5094 for TMCTS.

$$mg/m^3 = ppm*MW/24.45 = 100*240.5/24.45 = 983.6$$

The ITSL was based on the equation from Rule 232(1)(d): ITSL from 7-day NOAEL, as follows:

$$ITSL = \frac{NOAEL}{35\,x\,100}\,x\,\frac{hours\,exposed\,per\,day}{24\,hours\,per\,day}$$

Because of the longer duration of the study, 28-days instead of the 7-day duration as prescribed in Rule 232(1)(d), a reduction of uncertainty for extrapolation to chronic exposures is expected. Therefore, the uncertainty factor of 35 was reduced to 20 (from 3.5 to 2 for subacute to subchronic and retaining the factor of 10 for subchronic to chronic). Note that the factor of 100 is composed of uncertainty factors of 10 for extrapolation of animal data to human data (interspecies) and 10 to account for sensitive subpopulations in the human population (intraspecies). The derivation of the ITSL for TMCTS is shown as:

ITSL = (984 mg/m^3)/(20×100) × 6/24 × 1000 µg/mg
ITSL = 0.492 × 0.25 × 1000 µg/mg
ITSL = 0.123 × 1000 µg/mg
ITSL = 100 µg/m^3 with annual averaging time (rounded to 1 significant figure)

Pursuant to Rule 232(2)(c), the averaging time is annual.

References

CompTox. 2021. DTXSID10870958. CompTox Chemicals Dashboard. https://comptox.epa.gov/dashboard/dsstoxdb/results?search=2370-88-9

DEQ. 1998. File for cyclic methyihydrogensiloxane, d4 (CAS #2370-88-9). Michigan Department of Environmental Quality. Interoffice Communication. By Catherine Simon, Supervisor, Air Quality Division, Toxics Unit. Date: Nov 10, 1998.

ECHA. 2021. Registration Dossier for 2,4,6,8-tetramethylcyclotetrasiloxane. European Chemical Agency. Helsinki, Finland. European Commission regulation: Registration, Evaluation, Authorisation and Restriction of Chemicals. https://echa.europa.eu/registration-dossier/-/registered-dossier/15844/

MICHIGAN DEPARTMENT OF ENVIRONMENTAL QUALITY

_____

INTEROFFICE COMMUNICATION

_____

November 10, 1998

TO: File for cyclic methylhydrogensiloxane, d4 (CAS #2370-88-9)

FROM: Cathy Simon, Supervisor, Toxics Unit, Air Quality Division

SUBJECT: Change in the Initial Threshold Screening Level (ITSL)

The ITSL for cyclic methylhydrogensiloxane, d4 (CAS #2370-88-9) has been changed from 0.04 µg/m³ to 0.1 µg/m³ based on an annual averaging time.

The change in the ITSL was made due to a revision in the State's air toxic rules which became effective on November 10, 1998. Previously, the ITSL had been set pursuant to Rule 232(i). This rule sets the ITSL at a default value of 0.04 µg/m³ (annual average) when no specific data are available to determine an ITSL. The November 10, 1998 revisions to the rules changed this default ITSL to a value of 0.1 µg/m³.

No updated review of the literature has been done since the ITSL was originally set at a value of 0.04 µg/m³, to determine if new data are available for this compound.

CAS:SLB

MICHIGAN DEPARTMENT OF ENVIRONMENTAL QUALITY

_____

INTEROFFICE COMMUNICATION

_____

August 14, 1996

TO: File for Cyclic methylhydrogen siloxane, D4 (2370-88-9)

FROM: Dan O'Brien, Toxics Unit, Air Quality Division

SUBJECT: Initial Threshold Screening Level for cyclic methylhydrogensiloxane, D4

The initial threshold screening level (ITSL) for cyclic methylhydrogensiloxane, D4 is 0.04 µg/m³ based on an annual averaging time.

The following references or databases were searched to identify data to determine the ITSL: AQD chemical files, IRIS, HEAST, ACGIH TLV Booklet, NIOSH Pocket Guide to Chemical Hazards, RTECS, NTP Management Status Report, EPB Library, IARC Monographs, CAS On-line and NLM/Toxline (1967 - May 1, 1996), CESARS, Handbook of Environmental Data on Organic Chemicals, Patty's Industrial Hygiene and Toxicology, Merck Index and the Condensed Chemical Dictionary. In addition, a request was made (5/10/96) to the Dow Corning Corporation for provision of any relevant toxicological data, but none were available.

The only toxicological data found in any of our searches was a single EPA document (EPA, 1993) which described Salmonella and Escherichia coli mutagenicity assays. The chemical was tested in five strains, with and without Aroclor-induced rat liver microsomes. No positive responses were observed either with or without metabolic activation in any strain at either 100 or 5000 µg/plate.

No toxicological data specific to this chemical were found which could be used in the derivation of a screening level. Consequently, per section R 336.1232, Rule 232, subrule (1)(i) of Act 451, the ITSL for cyclic methylhydrogensiloxane, D4 = 0.04 µg/m³, and per rule 232, subrule (2)(a), an annual averaging time applies.

DO:slb